38. (1X Amended) The catheter of Claim 37, wherein the steroidal anti-inflammatory agent is selected from the group consisting of dexamethasone [dexamethasome] and beclomethasone.

44. (1X Amended) The method of Claim 43, wherein the steroidal anti-inflammatory agent is selected from the group consisting of dexamethasone [dexamethasome] and beclomethasone.

Remarks To The Amendments

Applicant has cancelled claims 40 and 42.

Claims 13, 27, 29, 33, 34 were amended to indicate that the polymer is intimately mixed with the anti-inflammatory agent. Support for the amendment can be found on page 13, lines 24-29:

> In one embodiment, the polymer of the tissue-contacting surface and an anti-inflammatory agent are intimately mixed either by blending or using a solvent in which they are both soluble (e.g., xylene for silicone and dexamethasone phospate). This mixture can then be formed into the desired shape and incorporated into the medical device or coated onto an underlying structure of the medical device. (page 13, lines 24-29 –emphasis added).

Claims 38 and 44 as follows were amended to correct the spelling of "dexamethasone."

Remarks To The Examination

Objections

Claims 38 and 44 were objected to because of the following informalities: "Dexamethasone" was misspelled. Appropriate correction was required.

Applicants have submitted corrections to the spelling of "dexamethaxone", and request that the objections to claims 38 and 44 be removed.

Rejections Under 35 USC § 103 – Chait In View of Stokes and Fearnot

Claims 13-19, 24, 27, 29, 33, 34, 36-39, 41, 43, and 44 were rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat. No. 5,727,555 (herein referred to as "Chait") in view of US Pat. No. 4, 711,251 (herein referred to as "Stokes") and US Pat. No. 5,609,629 (herein referred to as "Fearnot").

Chait was cited as a reference for teaching a catheter having an external fitting coupled to the proximal end of the catheter, and a catheter containing helical coils (col.4, lines 24-28). The examiner indicates that Chait fails to provide a catheter having a layer with an anti-inflammatory agent. However, the Examiner combines the teaching of Chait with the teachings of Stokes.

Stokes was cited for teaching an elongate body-inserted member with a drug imbedded in an outer non-porous silicone layer (Col. 4, lines 24-28). Stokes was also cited for teaching that the drug can be an anti-inflammatory agent, anti-thrombotic agent, or combination of the two (col. 1, lines 65-67).

In addition, Fearnot was cited for teaching a catheter (col. 6, line 25) with a drug imbedded in a non-porous layer 18, the drug specifically disclosed as dexamethasone (col. 8, line 66). Fearnot was also cited for teaching that the catheter can have heparin embedded in it (col. 8, line 49). Additionally, Fearnot was used as a reference for teaching that the layers can consist of about 0.5 to 2.0 mg/cm^2 of each heparin and dexamethasone, for a total of 1 to 4 mg/cm^2 of bioactive material (heparin and dexamethasone). The Examiner has also pointed out that at the top of page 12 of applicants' own specification it is disclosed that "Generally it is believed however, that less than about 1 mg of an anti-inflammatory agent per square centimeter of surface area of a polymer-contacting surface can be used to produce the advantageous results described herein." The ranges

taught by Fearnot are consistent with applicants' own; therefore. it would have been obvious to form the bioactive layers with the claimed weight percentages since it appears as though the same amounts of the bioactive materials are deemed to be suitable for this purpose by those skilled in the art.

Thus, the Examiner contends that after reading Chait, in view of Stokes and Fearnot, it would have been obvious to one of ordinary skill in the art to form the catheter of Chait with the layered structure of Stokes with the concentration ranges of Fearnot. The examiner further contends that since Stokes discloses the drugs so broadly, it would have been obvious to one of ordinary skill in the art to choose an appropriate anti-inflammatory.[1] Applicants respectively traverse.

Applicants contend that the Examiner has not established a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, the examiner must show:

1) that the prior art references relied upon teach or suggest all the claim limitations;

2) some suggestion or motivation to modify or combine information in the prior art or pool of knowledge available to one of ordinary skill art at the time of filing the application; and

3) a reasonable expectation of success in modifying or combining the prior art teachings.

In re Fine, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988), citing In re Lalu, 747 F.2d 703, 705, 223 U.S.P.Q. 1257, 1258 (Fed. Cir. 1984). "Obviousness is tested by what the combined teachings of the references would have suggested to those of ordinary skill in the art." In re Fine, at 1599, citing In

[1] The Examiner further indicated that the methods of claims 27 and 29 only add the step of inserting the catheter as taught by Chait. Similarly, the Examiner contended that the methods claimed in claims 33 and 34 relate simply to the assembled structure and that there are no specifics about the assembly. Thus, the Examiner contended it would have been obvious to one of ordinary skill in the art that the components of Chait can be put together in order to have the structure shown.

re Keller, 642 F.2d 413, 425, 208 U.S.P.Q. 871, 881 (C.C.P.A. 1981). Prior art references do not establish obviousness "absent some teaching or suggestion supporting the combination." ACS HosD. Svs.. Inc. v.Montefiore Hosp., 732 F.2d 1572, 1577, 221 U.S.P.Q. 929, 933 (Fed. Cir. 1984).

First, applicants indicate that Chait taken in view of Stokes and Fearnot does not teach or suggest all the claim limitations. Fearnot teaches a coated medical device with a releasable bioactive layer; however, the release mechanism is accomplished by adding a porous coating layer positioned over a bioactive layer. Fearnot deposits the biomaterials on an underlying substrate such as applied by vapor deposition or plasma deposition.[2] There is no teaching that the materials are intimately mixed into the polymer as claimed.

Second, Chait in view of Stokes and Fearnot are not anticipatory because the cited references fail to teach the claimed limitation of the steroidal anti-inflammatory agent being present in a concentration of between 0.1% and 5% of the steroidal agent in the polymer (w/w). Although applicants' specification gives a suggested surface concentration of less than 1 mg of an anti-inflammatory agent per square centimeter, the applicants respectfully point out their claim is directed to an intimately mixed polymer and anti-inflammatory agent having between 0.1% and 5% of the steroidal agent in the polymer (w/w).

Contrary to the Examiner's assertion, Fearnot only teaches a surface concentration range of "1 to 4 mg of bioactive material per cm^2 of the gross surface area of the structure."[3], which is different and considerably higher than the concentration ranges claimed by applicants. Applicants indicate that comparison of surface concentrations of the active agent does not respectfully equate to total concentrations (w/w) when intimately mixed in

[2] US 5,609,629, Col. 3, lines 22-29.
[3] US 5,609,629, Col. 4, lines 41-47.

the polymer as claimed. For example, the Examiner's attention is directed to Table 3, page 45, where one can see that a 1% dexamethasone/ polyurethane composition (w/w) equates to a surface concentration of 0.09 to 0.08 dexamethasone/cm^2 and 5% dexamethasone (w/w) equates to a 0.6 to 0.5 % dexamethaxone/cm^2. This represents an approximately ten-fold lower concentration over the Fearnot surface concentrations.

→ actually less than 2X

As previously mentioned, Fearnot teaches a coated medical device with a releasable bioactive layer; however, the release mechanism is accomplished by adding a porous coating layer positioned over a bioactive layer. Applying Chait in view of Stokes and Fearnot, therefore, would not provide one a reasonable expectation of success for finding the claimed dosage ranges. The present invention differs from the combined teaching of Chait and Fearnot in that polymers of the device are intimately mixed with the therapeutic agent(s). Using the concentration ranges of Fearnot, one would not expect the substantially lower concentration ranges of applicants to work. In fact, because most of the drug is contained internally in the polymer and not on the surface, one would probably expect to try higher concentration ranges to achieve an effective concentration. It should be pointed out that Fearnot provides no experimental testing to guide one skilled in the art. Although no more is required of Fearnot, all that is provided is the assertion that heparin having a surface concentration of 1 to 4 mg per cm^2 one can achieve a release rate of 0.1 to 0.5 mg/cm^2 per day.[4] This contrasts with the data appearing in Figure 7 showing that the initial burst of dexamethasone release was maximally in the order of 1.6 to 19.5 μg of dexamethasone per cm^2 of material (which declines thereafter). Even given the inherent problems of making such comparison between the two experiments, it does

[4] US 5,609,629, Col 10., lines 32-35.

further indicate the difference between applicants' invention and that suggested by the cited references.

Applicants further maintain that neither Chait, Stokes, nor Fearnot singularly or collectively provide a suggestion or motivation to combine their teachings to produce applicants' claimed invention. As such, the references cannot properly be combined. Further, applicants also have demonstrated that even if the references are combined there is no expectation of success in obtaining the claimed invention.

In summary, applicants assert that the combination of Chait, Stokes, and Fearnot does not establish a *prima facie* case of obviousness. In view of applicants' amended claims and arguments, they respectfully request that the present rejection under 35 U.S.C. §103 pending against claims 13-19, 24, 27, 29, 33, 34, 36-39, 41, 43, and 44 be removed.

35 U.S.C. § 103 - Chait In View of Stokes, Fearnot and Hendriks

Claims 40 and 42 were rejected under 35 U.S.C. § 103 as being unpatentable over Chait in view of Stokes and Fearnot as applied to claims 13 and 29 above, and further in view of Hendriks et al. (US Patent No. 5,811,151 – herein referred to as "Hendricks").

Applicants have cancelled claims 40 and 42 rendering the present rejection moot.

Summary

In view of applicants' amendments and arguments, they respectfully request allowance of all pending claims and eagerly await a notice of allowance.

Respectfully submitted,

Kenneth J. Collier April 9, 2001

Kenneth J. Collier
Attorney/Agent for Applicant(s)
Registration No. 34,982
Phone: 763-505-2521

Medtronic, Inc.
Patent Department
710 Medtronic Parkway NE
Minneapolis, MN 55432-5604

AMENDED CLAIMS

Version with Markings To Show Changes Made

In the Claims

13. (3X Amended) An indwelling catheter comprising:

an elongate body having a proximal end, a distal end, a tissue-contacting surface, and at least one interior lumen therethrough; and

an external fitting coupled to the proximal end;

wherein the tissue-contacting surface of the elongate body comprises a polymer in which a steroidal anti-inflammatory agent is intimately mixed [in intimate contact], the steroidal anti-inflammatory agent being present in a concentration of between .1% and 5% of the steroidal agent in the polymer (w/w).

27. (3X Amended) A method of modulating tissue encapsulation of an indwelling catheter comprising implanting the indwelling catheter into a patient, wherein the indwelling catheter comprises:

an elongate body having a proximal end, a distal end, a tissue-contacting surface, and at least one interior lumen therethrough; and

an external fitting coupled to the proximal end;

wherein the tissue-contacting surface of the elongate body comprises an overcoating of a polymer in which a steroidal anti-inflammatory agent is intimately mixed[incorporated] at a concentration of between .1% and 5% of the steroidal anti-inflammatory agent in the polymer (w/w).

29. (3X Amended) A method of modulating degradation of an indwelling catheter comprising implanting the indwelling catheter into a patient, wherein the indwelling catheter comprises:

an elongate body having a proximal end, a distal end, a tissue-contacting surface, and at least one interior lumen therethrough; and

an external fitting coupled to the proximal end;

wherein the tissue-contacting surface of the elongate body comprises a polymer intimately mixed [in intimate contact] with a steroidal anti-inflammatory agent and wherein the solid weight of the steroidal anti-inflammatory agent is between .1% and 5% of the total solid combined weight of the polymer and the steroidal anti-inflammatory agent.

33. (3X Amended) A method of making an indwelling catheter comprising:

providing an elongate body having a proximal end, a distal end, a tissue-contacting surface, and at least one interior lumen therethrough; wherein the tissue-contacting surface comprises an overcoat of a polymer intimately mixed with[in which] a steroidal anti-inflammatory agent [is incorporated] at a concentration of between .1% and 5% of the steroidal anti-inflammatory agent in the polymer (w/w); and

coupling an external fitting to the proximal end of the elongate body.

34. (2X Amended) The method of claim 33 wherein the step of providing an elongate body comprises intimately mixing the steroidal anti-inflammatory agent with the polymer in a solvent and applying the mixture to the elongate body to form a tissue-contacting surface.

38. (1X Amended) The catheter of Claim 37, wherein the steroidal anti-inflammatory agent is selected from the group consisting of dexamethasone [dexamethasome] and beclomethasone.

[40. The catheter of Claim 13, wherein the steroidal anti-inflammatory agent is covalently bonded to the polymer of the tissue contacting surface.]

[42. The method of Claim 29, wherein the steroidal anti-inflammatory agent is covalently bonded to the polymer of the tissue-contacting surface.]

44. (1X Amended) The method of Claim 43, wherein the steroidal anti-inflammatory agent is selected from the group consisting of dexamethasone [dexamethasome] and beclomethasone.